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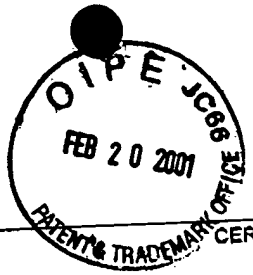

CERTIFICATE OF MAILING
37 C.F.R. 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231, on the date below:

2/14/01
Date

Gina N. Shishima

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Jack A. Roth

Serial No.: 09/447,681

Filed: November 23, 1999

For: ADENOVIRUS p53 COMPOSITIONS AND METHODS

Group Art Unit: 1632

Examiner: Crouch, D.

Atty. Dkt. No.: INRP:003--2

DECLARATION OF LOUIS ZUMSTEIN, PH.DUNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, Louis Zumstein, Ph.D., declare the following:

1. I am the Director of Research at Introgen Therapeutics in Houston, Texas. I have a Ph.D in Biochemistry and Molecular Biology from Harvard University. I have done extensive research on tumor suppressor genes, including p53, and their delivery to cells via viral vectors. I have authored five scientific papers on these topics. My *curriculum vitae* is attached as Exhibit 1.

2. I am familiar with the level of skill of scientists working in the field of gene therapy as of the October, 1992 priority date of the referenced application.

3. I have read the specification and pending claims 66-70 (as amended) for the above-referenced case. Claim 66 reads, "An adenovirus vector comprising a wild type p53 gene under the control of a promoter." Claim 67 reads, "The vector of claim 66, wherein the promoter is a CMV promoter. Claims 68-70 cover other promoters, specifically β-actin, SV40, and RSV. Claim 71 reads, "The vector of claim 66, wherein the wild type p53 gene is a human gene." A copy of these claims are attached as Exhibit 2.

4. From reading the specification, it is clear to me that had a person skilled in molecular biology and tumor suppressor genes read this specification in October of 1992, it would readily described to such a person an adenoviral vector encoding the p53 gene under a promoter, including a CMV, β-actin, SV40, and RSV promoter. This understanding is supported by the specifications on page 6, lines 33-35, which states "Another important 'oncogene' is the gene encoding p53....one of the most common targets for genetic abnormalities in human tumors"; on page 9 lines 22-23, which states "other vectors ... including adenovirus ...."; and page 15, lines 1-4, which states, "While the β-actin promoter is preferred the invention is by no means limited to this promoter, and one may also mention by way of example promoters derived from RSV...SV40...or CMV."

5. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable

by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

2/13/01
Date

Louis Zumstein, Ph.D.

Curriculum Vitae

Name: Louis A. Zumstein

Address: Introgen Therapeutics, Inc.
2250 Holcombe Boulevard
Houston, Tx 77030
(713) 610-4033 (w)
FAX: (713) 797-9913
l.zumstein@introgen.com

Industry Experience:

4/1999 to present

Director of Research
Introgen Therapeutics, Inc.
8080 N. Stadium Dr., Ste 1200
Houston, TX 77054

Supervising pre-clinical development of gene therapy products for oncology. as described below. Supervising clinical assay development for RPR/INGN 201.

3/1997 - 4/1999

Associate Director of Research
Introgen Therapeutics, Inc.
8080 N. Stadium Dr., Ste 1200
Houston, TX 77054

Supervised group gathering pre-clinical data on two products. Project leader for Introgen's second product, from vector construction through IND submission. This has involved directing and assembling pre-clinical experiments, in house and contract assay development, contract toxicology and bio-distribution studies, and coordination with Manufacturing, Clinical Affairs, Regulatory Affairs, and upper management, to define the fastest path to the clinic for this product.

3/1995 - 2/1997

Introgen Therapeutics, Inc.
8080 N. Stadium Dr., Ste 1200
Houston, TX 77054
Research Program Manager, Vector Development

Performed and supervised early production and process development work. Supervised clinical sample assay development, intimately involved in our Phase I HNSCC trial with RPR/INGN 201. Supervised group developing new vectors, and validating vectors from academic collaborators.

10/1993 - 2/1995

Sennes Drug Innovations, Inc.
8080 N. Stadium Dr., Ste 1200
Houston, TX 77054
Assistant Director of Research

Started as a bench scientist. By 2/95, was directly supervising our production group, and loosely supervising our cell biology/assay development group.

Education:

1973 - 1975	University of Miami, FL
1975 - 1977	Florida State University, Tallahassee, FL B. S. in Biology, magna cum laude
1978 - 1986	Harvard University, Cambridge, MA Department of Biochemistry and Molecular Biology Professor James C. Wang, Advisor Ph.D. in Biochemistry

Postdoctoral training:

1986 - 1987	Department of Genetics, Harvard Medical School and Department of Molecular Biology Massachusetts General Hospital, Boston, MA "Use of DNA catenanes to study transcriptional activation in *S. cerevisiae*."
1988 - 1991	Department of Biological Sciences Stanford University, Stanford, CA "Mutational analysis of NodD, a master regulatory transcriptional activator of alfalfa nodulation by *Rhizobium meliloti*."
1991 - 1993	Department of Biochemistry Baylor College of Medicine, Houston, TX "Direct mechanistic coupling between RNA splicing and transcription."

Awards and Honors:

1977	Phi Beta Kappa Florida State University, Tallahassee, FL
1988 - 1991	NSF Postdoctoral Research Fellowship in Plant Biology

Publications:

Sternglanz, R., DiNardo, S., Voelkel, K.A., Nishimura, Y., Hirota, Y., Becherer, K., Zumstein, L. and Wang, J.C. (1981) Mutations in the gene coding for *Escherichia coli* DNA topoisomerase I affect transcription and transposition. Proc. Natl. Acad. Sci. USA *78*, 2747-2752.

Margolin, P., Zumstein, L., Sternglanz, R. and Wang, J.C. (1985) The *Escherichia coli supX* locus is *topA*, the structural gene for DNA topoisomerase I. Proc. Natl. Acad. Sci. USA *82*, 5437-5441.

Zumstein, L. (1986) Studies of *Escherichia coli* DNA topoisomerase I. Ph.D. Thesis. Cambridge, Massachusetts: Harvard University.

Zumstein, L. and Wang, J.C. (1986) Probing the structural domains and in vivo function of *Escherichia coli* DNA topoisomerase I. J. Molec. Biol. *191*, 333-340.

Clayman, G. L., El-Naggar, A. K., Lippman, S. M., Henderson, Y. C., Frederick, M., Merritt, J. A., Zumstein, L. A., Timmons, T. M., et. al. (1998). Adenovirus-Mediated p53 Gene Transfer in Patients With Advanced Recurrent Head and Neck Squamous Cell Carcinoma. J. Clinic. Oncol. *16*, 2221-2232.

Zumstein, L. A., and V. J. Lundblad (1999). Telomeres: has cancer's Achilles' heel been exposed? Nature Medicine. *5(10)*, 1129-1130.

Jacobberger, J. W., Sramkoski, R. M., Zhang, D., Zumst in, L. A., Doerksen, L. D., Merritt, J. A., Wright, S. A., and K. E. Shults (1999). Bivariate Analysis of the p53 Pathway to Evaluate As-p53 Gene Therapy Efficacy. Cytometry. *38 (5)*, 201-213.

Kawabe, S., Munshi, A., Zumstein, L. A., Wilson, D. R., Roth, J. A., and R. E. Meyn (2000). Adenovirus-mediated wild-type p53 gene expression radiosensitizes non-small cell lung cancer cells but not normal lung fibroblasts. Int. J. Radiation Biology. In press.

Paula Ghaneh, P., Greenhalf, W., Humphreys, M., Wilson, D., Zumstein, L., Lemoine, N., and J. Neoptolemos (2000). Adenovirus mediated transfer of p53 and p16 results in pancreatic cancer regression in vitro and in vivo". Gene Therapy. Accepted.